UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

IN RE: VIAGRA PRODUCTS LIABILITY LITIGATION	MDL No. 1724 Judge Paul A. Magnuson
This document pertains to: ***Martin v. Pfizer*** ***Stanley v. Pfizer***	

EXPERT REPORT OF CHERYL BLUME Ph. D.

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Date

OUTLINE OF VIAGRA AND NON-ARTERITIC ISCHEMIC OPTIC NEUROPATHY REPORT

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1. Introduction and Background

My name is Cheryl Blume, Ph. D. I received my Ph.D. in Pharmacology and Toxicology from The West Virginia University Medical Center where I was a recipient of a pre-doctoral fellowship from the National Institute of Health. I am President of Pharmaceutical Development Group, Inc., a consulting firm specializing in pharmaceutical development and registration activities, located in Tampa, FL. I previously held several executive positions in pharmaceutical companies for over 20 years. Specifically, I served as the Vice President of Scientific Affairs for Mylan Laboratories, Inc. and as the Executive Vice President and Chief Operations Officer for Somerset Pharmaceuticals, Inc. I was also a member of the Board of Directors of Somerset. A copy of my CV is included as Exhibit 1.

I have been responsible for preclinical and clinical (Phases I-IV) programs associated with pharmaceutical product development and the securing of pre-marketing approvals for over 100 prescription pharmaceutical drugs from the U.S. Food and Drug Administration (FDA). These products include both new (brand name) and generic drug products. These responsibilities included the design, execution and interpretation of pivotal preclinical and clinical trials. I have also directed all phases of interactions with the FDA relating to the prosecution of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements to New Drug Applications (sNDAs) and the approval procedures. These include the collection and evaluation of postmarketing adverse medical events, the preparation of amplified product labeling, and the dissemination of updated product information to health care providers, patients and consumers. I have also been responsible for the regulatory review of promotional and educational materials for both brand-name and generic drug products.

Based on my education, training and experience, I have been asked to address the scientific and regulatory actions taken by Pfizer in the development, post-launch evaluations, labeling and marketing of Viagra (sildenafil), particularly as they relate to Non-Arteritic Ischemic Optic Neuropathy (NAION). The opinions provided in this report are expressed to a reasonable degree of scientific certainty.

I hereby reserve the right to supplement this report if additional information is provided. I charge $400/hour for document review and report preparation and $450/hour for deposition and trial testimony. A list of documents provided to me is included with Exhibit 2.

2. Regulatory Responsibilities of Pharmaceutical Manufacturers

Pharmaceutical manufacturers must comply with specific regulatory procedures and regulations when developing and marketing drug products. For example, before a new drug product can be marketed in the United States, pharmaceutical manufacturers are required to independently conduct a wide variety of preclinical (animal) and clinical studies to support their pre-marketing applications (NDAs). These include studies designed to assess the clinical safety and efficacy of their drugs in the patient populations for whom the drug will be prescribed. Sponsors often additionally examine specific patient populations to determine if their proposed drug may have selective safety concerns in these patients. The U.S. FDA does not and cannot independently guarantee the safety of all pharmaceutical products. An FDA approval also does not guarantee that a drug product will be found to be safe for all time and for all purposes. There have been several drugs that were approved by the FDA and then later withdrawn from the U. S. market because of unanticipated emergent adverse medical events.

The FDA relies upon the manufacturer of a new drug product to conduct appropriate clinical trials. As such, the manufacturer controls all critical elements relating to these trials. The manufacturer supplies the funding for the clinical trials as well as the medications employed in these trials. The drug manufacturer also selects and monitors the clinical investigators who conduct the trials. All clinical trial data are submitted directly to the manufacturer. Similarly, the required preclinical trials are also conducted and controlled by the manufacturer. When completed, the preclinical and clinical trial data are compiled and reported to the FDA by the manufacturer.

Based on the information provided by the pharmaceutical manufacturer, the FDA then reviews the submitted preclinical and clinical data to determine if the proposed drug product is safe and effective. As part of the NDA approval process, the FDA evaluates the professional labeling ("package insert or label") to be provided with the new drug product. This labeling is developed based on the information provided by the sponsor

and should be designed to convey all necessary prescribing and safety-related information. Pharmaceutical manufacturers are also required to provide FDA with reports and analyses of updated safety-related information following FDA's approval of an NDA for a new drug product.

Frequently, critical safety concerns are not observed until after an approved product has been commercially launched. There are several reasons for the delayed appearance of adverse medical events, foremost of which is that a relatively small number of patients (usually only up to a few thousand) are exposed to a new drug before it is approved. As such, only the most frequently occurring adverse events will be observed. Following approval, and use of the drug by a much larger population, less frequently-occurring adverse events will then be evidenced.

A second reason contributing to the delayed appearance of certain events relates to the relatively homogenous patient populations enrolled in pre-approval clinical trials. Patients participating in these trials must meet strict inclusion criteria. Following drug approval, additional patient populations, including those with other concomitant illnesses and those receiving other drug products will be prescribed the drug. Not surprisingly, use of the drug in a larger and more diverse patient population often leads to the appearance of new adverse events, increases in the frequency of previously observed events and the emergence of new drug interactions.

FDA and international regulatory authorities specifically require pharmaceutical manufacturers to rigorously track and report worldwide adverse event information following the launch of a new drug. This surveillance is critically important for the safe use of a drug product. Experience has taught that pre-marketing clinical trial data provide only initial and preliminary safety information for a new drug product. As such, it is imperative that all sources of reported adverse events be closely monitored and fully evaluated and that any necessary follow-up studies are designed and conducted. Safety

data may be derived from a variety of sources including the manufacturer's internal studies, United States and foreign adverse event databases, spontaneous domestic and international adverse event reports and studies, ongoing United States and foreign trials, patient data repositories, the clinical and preclinical literature, international regulatory events and other available databases (see 21 CFR §314.80; 21 CFR §312.32(b); 21 CFR §312.33(f); Form FDA 356h; and March 2005 Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment).

Because the post marketing surveillance system provides safety data concerning real patients in a real world setting, it is a vital and integral component of the FDA's efforts to ensure the continued safety of marketed drug products. It is for this reason that the FDA relies on safety surveillance to track adverse drug experiences from the launch of a new drug product and throughout its entire marketing lifespan. Unfortunately, the surveillance system captures only a fraction (approximately 1-10%) of the actual number of adverse event (FDA Presentation, Allen Brinker, M.D., Epidemiology Team Leader, Office of Surveillance and Epidemiology, CDER, December 14, 2006). It is therefore imperative that manufacturers closely monitor all available data, conscientiously review published literature, conduct necessary follow-up studies and fully explore all potential adverse events.

Several factors contribute to the low percentage of significant adverse medical events actually reported to the FDA and to other authorities. A major factor is that many health care providers do not associate a patient's complaints or symptoms with a drug-related adverse event. Often times the new event is simply considered a component of the patient's medical condition or an unrelated concomitant illness. This is particularly likely to occur if representatives of the drug manufacturer fail to share all available label information with prescribers or make untrue or scientifically unbalanced presentations to prescribers. It is therefore critically important that drug manufacturers fully alert prescribers to potential adverse events and safety concerns with their products in all promotional materials. Additionally, adverse event reporting may be diminished when

multiple specialty physicians are independently treating and managing a patient's medical care and resultant adverse drug experiences.

Another factor contributing to the low reporting rate of adverse events is that many health care providers are simply unaware of the various programs developed to receive this information. Pharmaceutical organizations should assist FDA with their ongoing efforts to promote this important exchange of information. Finally, the great majority of adverse event reports are sent to and reviewed by the manufacturer of the drug product, who is then required to submit data relevant to these reports to the FDA. If a manufacturer inaccurately, incompletely, or inarticulately submits adverse event reports and subsequent analyses, the FDA may not fully appreciate an emerging or changing safety profile associated with a drug product. Obviously, if information concerning a particular adverse event is not reported to FDA or it is reported in a way that is misleading or inaccurate, FDA will not be able to make timely and appropriate regulatory decisions.

FDA's post-marketing surveillance requirement is in place to detect new safety signals associated with the use of a drug product, signals that may not have been detected in the pre-marketing clinical trials. The system also detects increases in the frequency or severity of previously identified events. If there is a reasonable association between the event and the drug product, additional or intensified labeling warnings relating to the newly identified event can be enacted. Once a signal is detected, the specific adverse events should be fully and quickly evaluated to determine if a new patient safety risk has been identified. The sponsor is then required to review this information with the FDA to determine if additional scientific studies and regulatory actions are needed to address safety concerns. FDA notes that additional investigation of safety signals can be accomplished with randomized and non-randomized observational clinical studies. Examples of observational studies include pharmacoepidemiologic studies, registries, and surveys. FDA encourages sponsors to choose the best method to detect the specific safety signal and to communicate their plans with the Agency (March 2005 Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment). If the manufacturer and/or the FDA consider the new signal sufficiently serious, the drug

product may be restricted to certain patients or even withdrawn from the U.S. marketplace.

Importantly, the duty to detect and promptly act upon "signals" in post marketing surveillance is that of the manufacturer. The manufacturer must promptly alert physicians, patients and the FDA when a potential danger exists. Although FDA may also receive reports of Adverse Drug Events (ADE), the FDA does not have the resources to properly evaluate and act upon reports concerning thousands of marketed products. The first line of defense falls to the manufacturer of the product, and if the manufacturer fails in its duty, serious injury or death may occur. There is no magic number for the number of events needed to precipitate immediate action by the NDA holder. It does not have to include an explosion of events. There are examples of labeling changes and Dear Health Care Professional letters issued based upon the manufacturer's receipt of only two or three events.

There are obligations to report safety related information occurring outside the United States (21 CFR §314.80; 21 CFR §312.32(b); 21 CFR §312.33(f)). Manufacturers also have an obligation to report significant international labeling changes to the FDA (21 CFR §314.80; March 2001 Guidance for Industry, Postmarketing Safety Reports for Human Drugs and Biological Products Including Vaccines). The reporting of worldwide events is critically important because most safety issues are not dependent on national or regional related parameters.

Pharmaceutical manufacturers are required to continually amend their package inserts, professional labeling and promotional materials in response to new safety information. Such safety information includes new ADEs or changes in the severity or frequency of previously identified events. These data may be derived from post marketing reports, reports from clinical trials, ongoing studies or the clinical literature. Product information and labeling must be immediately modified and disseminated when serious clinical events are reported (21 CFR §314.70; April 2004 Guidance for Industry, Changes to an

Approved NDA or ANDA). All efforts must then be taken to ensure that the necessary information is expeditiously conveyed to health care professionals and consumers.

It cannot be stressed strongly enough that it is the pharmaceutical manufacturer who bears the obligation and responsibility to assure the safety of its marketed pharmaceutical products. The FDA does not have the authority, mission or resources to independently seek out and identify all safety issues involving all marketed drugs products. FDA resource limitations are well known, and dictate very limited post-marketing safety assessments. In fact, prominent drug safety issues involving recently withdrawn products have called into question the FDA's ability to adequately monitor the safety of marketed pharmaceutical products and have prompted the Agency to seek a significant increase in budgeted resources for the Office of Drug Safety (ODS). The FDA has publicly stated that budget increases are necessary to enhance the Agency's surveillance capability and to counter the perception that FDA is unable to ensure the safety of marketed drugs (Institute of Medicine Report, September 2006). Unfortunately, until this funding occurs, the responsibility for safety monitoring of drug products continues to fall squarely on the NDA sponsors.

3. Erectile Dysfunction Drugs and NAION

Viagra® (sildenafil) was the first drug approved (1998) in the Unites States for the treatment of erectile dysfunction. The therapeutic effect of Viagra is mediated via inhibition of phosphodiesterase-5 (PDE-5) resulting in enhanced nitric oxide (NO) production and increased levels of cyclic GMP in the corpus cavernosum leading to smooth muscle relaxation and increased blood flow. Viagra can also inhibit other isoforms of PDE, including PDE-6 (found in the retina) a process which may produce color vision abnormalities observed with the drug (Gonzalez et al., 1999).

Following oral administration, Viagra is rapidly absorbed and the maximum plasma concentration is reached within 30-120 minutes. Subjects are advised to take Viagra 30-60 minutes prior to sexual activity and the effect of Viagra on erectile function lasts for 4 hours after dosing (Eardley et al., 1999). Primarily metabolized by the cytochrome P450 enzyme CYP 3A4, Viagra is converted to an N-desmethyl metabolite which accounts for approximately 20% of its pharmacologic activity. Both Viagra and its metabolite have a plasma half-life of 4 hours although increased plasma levels are experienced in a variety of patient populations including subjects over 65 years of age and patients with hepatic or sever renal complications (Viagra Product Labeling).

A review of the adverse events observed during worldwide pre-marketing clinical trials (18 randomized trials involving 2722 subjects exposed to sildenafil; Morales et al., 1998) revealed that the most frequently occurring adverse events were headache (16% vs. 4% in the placebo group); flushing (10% vs. 1%); dyspepsia (7% vs. 2%); nasal congestion (4% vs. 2%); and abnormal vision (3% vs. 0%). Abnormal vision events included blurred vision, increased light sensitivity and impairment of color discrimination (blue tinge to vision). A variety of cardiovascular parameters were also influenced by Viagra administration. These included cardiac output, reduced blood pressure and synergistic interactions with cardiovascular drug products. Due to potentiation of the effects of exogenously administered organic nitrates leading to clinically significant reductions in blood pressure (observed in Phase I studies), use of Viagra is contraindicated in patients

taking these agents. Vasodilatory actions may underlie several adverse events associated with Viagra use (dizziness, headache, nausea).

Soon after product launch, Pfizer quickly became aware of additional ophthalmologic adverse events associated with Viagra from a variety of sources and adverse event databases. Dr. Hans-Walter Roth, a German ophthalmologist, reported a series of 12 cases (June-July 1998) in which patients taking Viagra experienced a variety of serious adverse events ranging from increased ocular pressure to blindness (Bates #'s 003165835; 003000726-42; 003165966-92). Additionally, soon after the launch of Viagra in 1998, Public Citizen asked FDA to include stronger warnings in the Viagra label related to color aberrations, increased sensitivity to light and blurred vision in (98P-0561). In their October 2005 Citizen Petition (2005P-0423), this group requested the addition of a Black Box for all ED drugs regarding risk of blindness and dissemination of a Dear Doctor letter. Public Citizen also provided a review of reports of Ischemic Optic Neuropathy (ION) in the FDA's Adverse Event Reporting System (AERS) database. During the period between January 1, 1998 and December 31, 2004, Viagra was associated with the highest number of ION reports (19%) in the AERS database across all reported drug products. Further, sixty-two potential cases of Non-Arteritic Ischemic Optic Neuropathy (NAION) associated with the use of PDE-5 inhibitors were also reported to the FDA AERS database during the period January 1, 2004 and October 31, 2006 (Danesh-Meyer et al., 2007). Throughout its marketing period Viagra has maintained the lead sales position among the three approved drugs.

A number of case reports published in the medical literature demonstrate an association between the use of phosphodiesterase-5 (PDE-5) inhibitors and Non-Arteritic Ischemic Optic Neuropathy (NAION). Non-Arteritic Ischemic Optic Neuropathy (NAION) refers to optic nerve damage (and visual disturbances, including blindness) resulting from poor blood flow (ischemia) to the anterior part of the optic nerve, also called the optic nerve head. Ischemic optic neuropathy can be produced by giant cell arteritis (Hayreh et al., 1998), can occur spontaneously in patients possessing one or more of a number of risk factors, and has also been associated with erectile dysfunction drugs such as Viagra. The

first such case was published in 2000 (Egan and Pomeranz, 2000) describing a 52 year-old man developing optic neuropathy soon after the ingestion of Viagra (50 mg). Soon after this (October 2000), Dr. Pomeranz presented an abstract describing 5 cases of NAION in association with the use of Viagra. These findings were eventually published in March 2002 (Pomeranz et al., 2002).

While Pfizer was aware of these NAION cases in 2000, their response seemed to focus on deflecting the negative publicity which they knew would result (Bates #'s 003 211665-75; 003 085962; 002 184207) rather than initiating an update to the product labeling or performance of the necessary epidemiologic study required to determine the relatedness of this adverse event to the drug's use. Pfizer did sponsor several studies examining the effects of sildenafil (Viagra) on a number of ophthalmologic parameters (*i.e.*, ocular circulation, intraocular pressure and visual function - Sponsel et al., 2000; Yajima et al., 2000; Grunwald et al., 2001; 2001a; 2002; Birch et al., 2002; Jagle et al., 2004) and found no significant adverse effects. However, the small patient populations examined in these studies consisted primarily of healthy volunteers and the dosing regimens employed were not reflective of real-world use (*i.e.*, use of Viagra for several months to years). Seven additional NAION cases were published by Dr. Pomeranz in 2005 (Pomeranz and Bhavsar, 2005). Although this represented further support for the need of a definitive epidemiologic study, Pfizer continued to providing potential reasons (*i.e.*, co-morbid conditions) why the reports may not be represent an effect of Viagra (Bates # 002 184799).

As such, Pfizer's "Response to Press Release and News Story Regarding Viagra and Non Arteritic Anterior Ischemic Optic Neuropathy (NAION)" (Bates # 002 0184207) minimized the Viagra-NAION association and noted several reasons to overlook Viagra as a risk factor in the onset of NAION:

- "no reason to believe that Viagra DECREASES blood flow to the vessels supplying the optic nerve head."

- Several Pomeranz case reports "...have aspects to their descriptions which must be considered suspect when suggesting a causal association between the development of NAION and the use of Viagra."

- "Significant risk factors for vascular disease and/or NAION were described for several patients, including...diabetes, coronary artery disease, hypercholesterolemia, smoking, and a previous episode of AION in the opposite eye with recent visual difficulties before starting to take Viagra."

- "...patients' age (52, 69, 42, 62, 59) and male gender provide two well known risk factors for the development of vascular disease, regardless of whether or not they had additional cardiovascular risk factors."

- "...two of these cases, the patients were on Viagra for long periods of time (15 months in one case, 2 years in another) with no prior episodes of AION."

- "...a delay of 2 days following the suspect dose of Viagra before a visual field loss was reported (although eye pain occurred the day following Viagra use)"

Unfortunately, the campaign to minimize a serious adverse event was successful. By June 2005 a Pfizer employee wrote "Dear Viagra Team and Country Managers, After substantial media attention in the Viagra and NAION story over the weekend, we see now a regular and constant decline in the media reports across the world. However, it is critical that we maintain a consistent approach to this media-driven global issue" (Bates # 002 163800).

In June 2005, Pfizer attributed a "sudden drop in market growth is most likely due to the media reports of NAION which have caused alarm for both physicians and patients. While we believe that our efforts with physicians have been effective at reducing their concern, patient concern may continue for some time..." (Bates # 003 195297). By 2006, it was clear that Pfizer had developed a method for dealing with patient concerns: "Medical and clinical input will support marketing efforts...our business goal is to maintain the number one position in the ED market. This includes...focusing on reducing lapsing of Viagra patients" (Bates # 003 195241). In addition, Pfizer's plan to reduce the lapse in Viagra patients was to "Continue to support physician understanding of label changes such as alpha blocker and NAION as issues arise" (Bates # 003 195241).

The incidence rate of NAION has been estimated to be between 2.3 (Johnson and Arnold, 1994) and 10.3 (Hattenhauer et al., 1997) cases per 100,000 individuals. Notwithstanding this range, worldwide regulatory authorities have required the professional labeling for Viagra and other erectile dysfunction drugs to include warnings and precautions related to NAION events secondary to usage of these drug products. More recent studies have also examined the incidence of NAION in subjects using Viagra. While disparate results have been reported, the gravity of this event is obviously important in the consideration of benefit/risk assessments.

Using pooled safety data, the incidence of NAION was estimated to be 2.8 cases per 100,000 patient years of exposure to sildenafil (Gorkin et al., 2006). This was based on one observed case in 35,500 patient years of observation (Bates # 003 149656-7). Gorkin also noted that no cases of NAION were reported in 103 sildenafil trials conducted between 1993 and 2003 and no cases were reported in the International Mens Health Study, a prospective cohort of 3813 men receiving a sildenafil prescription in Germany, France, Spain or Sweden. A number of limitations are inherent with the Pfizer analysis. Pfizer has told FDA that difficulties in defining NAION cases precludes the performance of a case-control study, yet does not mention this as a potential in the Gorkin review. The clinical trials cited by Pfizer in support of their position were also not designed to assess NAION.

McGwin (2006) performed a case-control study to determine the association between Viagra and Cialis and NAION. Thirty-eight NAION cases were matched to 38 controls with no history of NAION. Although the overall odds ratio for Viagra in this study was not statistically significant (odds ratio 1.75, 95% confidence interval 0.48-6.30), a statistically significant association was observed in those patients with a history of myocardial infarction (odds ratio, 10.7; 95% confidence interval 1.3-95.8). Hypertensive men using Viagra or Cialis also had an increased odds ratio for NAION (6.9; 95% CI 0.8, 63.6) but this was not statistically significant. The authors note that their study is small and as such, the overall statistical power was low. However, given the results observed

and the potential significance of the associated adverse events, these results should not be diluted or ignored.

Margo and French (2007) performed a study (retrospective cohort) with the purpose of determining the feasibility of a case-control study of PDE inhibitors and NAION. The relative risk of "possible" NAION among men prescribed a PDE inhibitor was 1.34 (95% confidence interval, 1.17-1.55). This relative risk is statistically significant. The authors noted that the results of their study demonstrated that a case control study examining the incidence of NAION in users of PDE-5 inhibitors was feasible.

Pfizer also was aware of reports of a number of ophthalmologic adverse events (including NAION) occurring in the United States as well as foreign countries. Significant numbers of these events can be found in their internal pharmacovigilance documents (Safety Updates and Periodic Safety Update Reports, July 1998 through December 2005; see *e.g.*, Bates #'s 003 016910; 003 016863; 003 016690; 003 016744; 003 016800; 003 016468; 003 016522; 003 016592; 003 016223; 003 216492; 003 197709; 003 197817; 002 035386; 003 205290; 003 140202). Numerous other internal documents demonstrate Pfizer's awareness of significant numbers of ophthalmologic adverse events including NAION; blindness; optic ischemic neuropathy; and visual disturbance (Bates #'s 003 144315-720; 002 162562; 003 155429-31; 002 164944-7). Indeed, one Sildenafil report (Bates # 003035631-89) notes that the reporting rate of optic neuritis nearly doubled between Periodic Safety Update Reports XI (1.1%) and XII (2%) and that "[N]onarteritic anterior ischemic optic neuropathy (NAION) ... codes to optic neuritis...". Indeed, a total of 92 reports of optic neuritis were contained in Viagra PSURs prepared by Pfizer during the period December 1997 through September 2002. All of these documents support Pfizer's awareness of the potential ophthalmologic risks involved with Viagra use as well as their reluctance to consider these events as possibly related to the drug.

Additional adverse ophthalmologic events in association with sildenafil (Viagra) use have also been published in the medical literature since soon after the launch of the product (Donahue et al., 1998; Vobig et al., 1999; Burton et al., 2000; Murata et al., 2000;

Tripathi and O'Donnell, 2000; Gabrieli et al., 2001; Luu et al., 2001; Balacco et al., 2003; Bertolucci et al., 2003; Allibhai et al., 2004; Jagle et al., 2004; Marsh et al., 2004; Quiram et al., 2005; Nawaiseh et al., 2006; Sowka et al., 2007; Fraunfelder and Fraunfelder, 2008).

The association of Viagra with a number of visually-related adverse events, ranging in scale from alterations in color vision to permanent loss of vision clearly suggests pharmacological perturbation of visual processes. Regarding the association between Viagra and NAION (and associated temporary or permanent loss of vision), several lines of evidence support the possibility of a drug-induced effect. A hypotensive effect of Viagra (Mahmud et al., 2001) resulting from vasodilatation of systemic blood vessels, may also occur in ocular blood vessels, resulting in crowding of the optic nerve and reduced blood flow to the optic nerve (compartment syndrome; Burde, 1993). Patients with underlying defects (small disc to cup ratio) may be more susceptible to this type of event. Further, most case reports of NAION describe a subject detecting loss of vision following waking. This may be consistent with Viagra exacerbating the normal reduction in blood pressure observed during sleep hours.

Results from animal studies also support the biologic plausibility of Viagra inducing NAION. A phosphodiesterase inhibitor produced biphasic effects on ocular blood flow (Hotta et al., 1998). Further, sildenafil also reduces retinal function in mice heterozygous for a mutation causing absence of the gamma subunit of rod PDE-6 (Behn and Potter, 2001). Chronic sildenafil exposure was also found to cause dilatation and congestion of the choroidal vasculature in rats (Vatansever et al., 2003) and a number of inherited retinal conditions are associated with elevated levels of cGMP due to reduced phosphodiesterase activity (LaVail et al., 1974; Farber and Lolley, 1976). Elevated cGMP levels can cause degeneration of photoreceptors when retinal cells are exposed to phosphodiesterase inhibitors in vitro (Ulshafer et al., 1980). Pfizer was aware of these later studies even prior to Viagra approval (Bates # 001 000762-8).

Thus, despite the continuing accumulation of additional NAION cases in the medical literature associated with PDE-5 inhibitors (Cunningham and Smith, 2001; Boshier et al., 2002; Dheer et al., 2002; Sinha et al., 2004; Akash et al., 2005; Escaravage et al., 2005; Bollinger and Lee, 2005; Gruhn and Fledelius, 2005; Peter et al., 2005), Pfizer chose to concentrate on reducing the negative effects on sales while ignoring the need to perform appropriate epidemiologic studies or adequately warn prescribers and their patients.

The continued accumulation of serious adverse ophthalmologic events associated with Viagra use and found in the medical literature, foreign and Unites States spontaneous adverse event databases and Pfizer's internal adverse event database should have prompted Pfizer to undertake a more thorough analysis of NAION-related events associated with the drug. Many of these adverse events were serious, including reports of blindness. These reports began to accumulate even prior to approval of Viagra in the United States or Europe and continue to the present day. Evidence was available to at least suggest a biologically-plausible mechanism for many of these events and more recent epidemiologic studies have suggested a potential role for Viagra in the development of NAION and related disorders. Despite the number and severity of these reports, Pfizer did not initiate the performance of a study examining the association of Viagra and NAION until October 2008 ('A Study to Assess Whether PDE5 Inhibitors Increase the Chance of Triggering the Onset of Acute NAION'; accessed at ClinicalTrials.gov, November 25, 2008). Had a study been initiated when it became apparent (soon after product launch) that ophthalmologic adverse events, many of which were serious, comprised a significant portion of the overall adverse event profile, it is likely the product labeling would contain more stringent language regarding NAION. Instead, Pfizer has repeatedly chosen to downplay the association, stating that spontaneous reports do not contain sufficient information to determine causality and that it would be too difficult to perform a study analyzing rates of NAION in Viagra users due to underlying risk factors.

4. Chronology of Viagra Regulatory Events (United States and Foreign)

U.S. Regulatory Chronology:

Three selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5) have been approved by FDA for the treatment of erectile dysfunction (ED). The first of these, Viagra (sildenafil citrate - Pfizer), was approved on March 27, 1998. Viagra is marketed as oral tablets with strengths of 25 mg, 50 mg, and 100 mg. In 2003, two additional agents Levitra (vardenafil; Bayer) and Cialis (tadalafil - Lilly) were approved the treatment of ED. Revatio (sildenafil citrate - Pfizer) was approved on June 3, 2005 for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. Revatio is marketed as 20 mg oral tablets.

Since its approval in 1998, FDA has released several documents noting vision problems with the use of Viagra. Concurrent with the Viagra approval, FDA published a Talk Paper (March 27, 1998) providing a short overview of the efficacy and safety of Viagra, noting that three percent of patients participating in the Viagra clinical trials reported changes in vision (mostly altered color perception). Mild and temporary visual changes were also noted in an additional document released by FDA at the time of product approval and addressed frequently asked questions concerning Viagra.

On August 13, 1998, FDA approved a patient package insert for Viagra. The approved insert listed blurred vision as less common side effect under the section Possible Side Effects. On November 24, 1998, FDA approved updated labeling changes for Viagra. In addition, FDA published an FDA Talk Paper relating to the Viagra labeling changes in response to postmarketing reports of serious cardiovascular adverse events. Additional labeling changes effected in November 1998 included information pertaining to the risk of sexual activity, transient decreases in blood pressure, patients not studied in the Viagra clinical trials and possible risks they may be exposed to when using the drug, and postmarketing reports of ocular adverse events including temporary vision loss/decreased

vision. Ocular adverse events would not be addressed again until the July 8, 2005 label revision. Complete label chronology is provided in Section 5.

Several Citizen Petitions were filed relating to the safety of Viagra. A Citizen Petition (98P-0561), submitted by Public Citizen on July 1, 1998 detailed the need to update the Viagra label for a number of different adverse events including adverse events related to cardiovascular function and vision. Public Citizen submitted another Citizen Petition on August 20, 1998 requesting a cardiovascular advisory committee meeting to discuss the use of Viagra in patients with increased CV risks. In their February 28, 2000 response to the 1998 Citizen Petitions, FDA stated that revised Viagra labeling addressed most of the stated Petition concerns. The request for an advisory committee meeting was denied at that time

In a Citizen Petition submitted on October 20, 2005, Public Citizen (2005P-0423) requested that FDA require Pfizer add a Black Box to the Viagra label relating to NAION and risk of blindness. The Citizen Petition noted that Viagra was the top drug product reported with NAION events in the U.S. AERS database. Pfizer responded to the Citizen Petition (December 20, 2005) by stating that NAION events are rare and have already been addressed by FDA. To date, FDA has not officially finalized their review of the pending Petition.

As early as January 2004, an FDA safety evaluator from the Office of Drug Safety concluded that NAION was an important safety issue for Viagra users (Citizen Petition 2005P-0423). On March 1, 2004, the FDA safety evaluator submitted her initial draft to her supervisor that was finalized and submitted to the Office of New Drugs on April 26, 2004 (see Citizen Petition 2005P-0423), noting:

> *The labeling for sildenafil should be updated to include a precaution and warning about the potential increased risk of non-arteritic AION resulting in permanent visual loss with the use of sildenafil in patients with vascular risk factors (such as hypertension, diabetes, hypotension) or optic disks anatomically predisposed to non-arteritic AION. Ophthalmologists and optometrists should be encouraged to solicit information regarding sildenafil usage from male patients who have optic*

> *disks anatomically predisposed to non-arteritic AION. These patients should be made aware of the potential increased risk of non-arteritic AION and permanent visual loss with the use of sildenafil. This information should also be included in the patient package insert.* (from Grassley June 24, 2005 letter to Crawford)

On February 24, 2005, after reviewing recent data from post-marketing adverse events and surveillance reporting related to visual effects of Viagra, FDA requested that Pfizer place the following wording relating to NAION in the Viagra label:

> **POST-MARKETING EXPERIENCE**
> **Special Senses:**
> *Non-arteritic anterior ischemic optic neuropathy (NAION), including permanent loss of vision, has been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for the development of NAION, including: low cup to disc ratio ("crowded disc"), diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to VIAGRA, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.*

Although there were repeated correspondences between Pfizer and FDA (May 26, 2005; June 16, 2005; June 24, 2005) relating to labeling changes, NAION was first added to the Viagra label in July 2005. In addition to the Postmarketing section, the NAION safety information was also added to the Precautions/Information for Patients section of the label, as seen below.

> **PRECAUTIONS**
> **Information for Patients**
> Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see **POST-MARKETING EXPERIENCE/Special Senses**).

Pfizer submitted to FDA a draft Dear Healthcare Professional Letter relating to the new vision-related additions to the Viagra label on August 4, 2005 (Bates #002190057). On September 8, 2005, FDA published an FDA Alert, an FDA Statement, and a Patient Information Sheet relating to NAION label changes for Viagra, Levitra and Cialis.

In a July 14, 2005 letter (Bates #002184600), FDA provided recommendations for the follow-up and reporting of postmarketing ophthalmologic adverse events that might reflect NAION. Additionally, in a July 28, 2005 letter (Bates #002184731), FDA requested that Pfizer re-examine data from controlled trials of PDE-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. FDA instructed Pfizer to prepare narrative summaries for a number of ophthalmologic adverse events, including optic ischemic neuropathy, optic neuropathy, retinal embolism, visual field defect, retinal artery occlusion, retinal artery thrombosis, retinal ischemia, visual acuity reduced, retinal vein occlusion and retinal vein thrombosis. FDA also requested that these events be further classified into one of three categories (NAION Events, Ophthalmologic Adverse Events Other Than NAION, and Events with Insufficient Information to Classify). Pfizer provided FDA with a list of these trials and a draft protocol for this analysis in September 2005; the final report was sent to FDA on May 3, 2006 (Bates #003289844-52).

On December 21, 2005, FDA sent a letter to Pfizer requesting "the conduct of a case-control study to determine whether use of PDE5 inhibitors is an independent risk factor for NAION" (Bates# 003289917). On March 17 2006, Pfizer claimed that given the substantial experience with sildenafil, a pharmacoepidemiology study examining NAION would not contribute additional information, and such a study would not be feasible (noted in Bates# 003289854). On April 11, 2006, FDA responded to Pfizer's claim that no feasible study could be conducted stating that various groups within FDA "continue to believe that a prospective case-control study is feasible and may provide valuable additional information towards determining the potential risk of PDE5 inhibitors as an independent contributor to NAION events, despite the experience of sildenafil to date." FDA refers Pfizer to a study conducted by McGwin et al. (2006) as the basis that a study could be conducted with reasonable sample size (Bates #003289854). On October 9,

2006, Pfizer submitted their proposed approach to investigate NAION with the use of Viagra (Bates #003215854). Pfizer began recruiting patients in October 2008 into their study "A Study to Assess Whether PDE5 Inhibitors Increase the Chance of Triggering the Onset of Acute NAION" (www.clinicaltrials.gov Identifier NCT00759174).

Following a March 17, 2006 FDA request that they submit all available cases of Central Serous Retinopathy reported in patients taking sildenafil citrate (Viagra® or Revatio®), Pfizer provided FDA with a report entitled "A Review of Sildenafil Adverse Events Reporting Central Serous Retinopathy in the Treatment of Erectile Dysfunction and Pulmonary Arterial Hypotension" on June 9, 2006. Along with this overview of available clinical and post-marketing sildenafil data, Pfizer also provided a summary of their pharmacovigilance activities relating to ophthalmologic events reported for sildenafil and a copy of the sildenafil Data Capture Aid (Bates# 003284103-11).

Additional non-vision safety concerns with Viagra have been reported by FDA and Pfizer since approval. In 1998 (updated on March 8, 2001), FDA published the Postmarketing Safety of Sildenafil Citrate (Viagra) relating to reports of death with Viagra users. This analysis noted 130 deaths in patients who had been prescribed Viagra (6 million prescriptions). Pfizer released a Dear Doctor Letter in May 1998 calling attention to the contraindicated use of nitrates and Viagra. FDA published new Viagra safety-related information with an FDA News press release and Questions and Answers on October 18, 2007 relating to the potential risk of sudden hearing loss and attendant new label changes. On November 2007, FDA published an FDA Summary and Information for Healthcare Professionals relating to sudden hearing loss and the use of ED drugs.

Viagra has been a successful drug product for Pfizer and has accounted for billions of dollars in revenue to Pfizer since its approval in 1998. For example, in 2003 alone, Viagra generated $1.9 billion in sales (http://www.cbsnews.com/stories/2004/01/26/health/main595785.shtml). Pfizer chose to conduct direct-to-consumer (DTC) marketing with Viagra, and, unfortunately, included

some advertisements that violated FDA regulations by omitting important safety information:

- February 2, 2000: DDMAC issued Untitled Letter (MACMIS # 8693) which stated in part "Valentine's Day broadcast advertisement for Viagra contains written and graphic representations and suggestions about Viagra yet fails to include information relating to Viagra's major side effects and contraindications."

- November 10, 2004: DDMAC issued another Untitled Letter (MACMIS # 12726) noting that "The TV ads fail to disclose the drug's indication, fail to include information relating to the major side effects and contraindications, and fail to make adequate provision for dissemination of the FDA approved or permitted package labeling, as required by 21 C.F.R. 202.1(e)(1) & (3). Moreover, the TV ads contain representations or suggestions that Viagra is better, more effective, or useful in a broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience."

- April 16, 2008: DDMAC issued a Warning Letter (MACMIS # 16225) relating to Viagra DTC ads that "fails to disclose any risk information associated with Viagra. Therefore, the video misbrands Viagra in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n). The video raises public health and safety concerns through its complete omission of risk information for Viagra by suggesting that Viagra is safer than has been demonstrated."

International Regulatory Chronology:

EMEA

On September 29, 1997, Pfizer submitted an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) for Viagra, through the centralized procedure. During a CPMP meeting on May 26 and 27, 1998, the CPMP issued a positive opinion for granting a Marketing Authorisation for Viagra. The CPMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on September 15, 1998.

The records suggest that Pfizer and European regulatory authorities were more interactive during the period of escalating NAION reports than that observed with Pfizer and the U.S. FDA. As early as March 5, 2000, the Pfizer submitted an application for a Type II variation for the implementation of additional information in the relevant parts of the various labels including the Summary of Product Characteristics, Labeling and Package Leaflet. These changes were in response to a request from the CPMP following review of PSURs and monthly line listings, indicating the need to update the SPC and Package Leaflet. The variation concerned the occurrence of eye disorders and additional relevant clinical safety information. The CPMP adopted a positive Opinion on May 25, 2000. The European Commission issued a favorable Decision on 12 September 2000. (See ©EMEA 2005 document)

After CPMP meetings on September 7-19, 2002, the EMEA informed Pfizer to "carefully monitor the occurrence of NAION and if appropriate submit a type II variation to add this adverse event to the SPC, e.g. at the time of the next PSUR." The EMEA suggested a statement comparable to "anterior ischemic optic neuropathy has been reported post marketing in temporal association with the use of VIAGRA" could be added to the SPC (Bates #002189869). On February 24, 2003, the EMEA notified Pfizer to continue to closely monitor for ocular events (Bates #003290697).

On June 21, 2005, CPMP requested Pfizer to add NAION to the Undesired Effects section of their Viagra label (Bates #003289937-9). CPMP also requested that Pfizer develop a Risk Management Plan to include proposals for studies to determine the underlying mechanism(s) for NAION.

On November 15, 2005, Pfizer added a warning to Viagra SPC relating to patients with previous episodes of NAION. NAION was also added to the Undesired Effects section of the SPC. (See ©European Medicines Agency, 2008)

On June 8, 2006, the Viagra SPC was updated to include a Contraindication for patients with previous episodes of NAION. In addition, the Special Warnings and Precautions and the Undesired Effects sections were altered relating to NAION. (See ©European Medicines Agency, 2008)

Other Interactions with Foreign Regulatory Authorities

On November 1998, the Australian Adverse Drug Reactions Bulletin announced the market introduction of Viagra and its Black Box for contraindicated nitrate use and cardiovascular risk factors. On June 2002, the Australian Adverse Drug Reactions Bulletin published a summary of three years of sildenafil adverse events. The article mainly discussed the cardiovascular events related to sildenafil use. In addition, 65 reports of abnormal vision were noted with Viagra use.

A review of the Periodic Safety Update Reports (PSURs) showed an increase in optic neuritis reporting rates to 1.1% in PSUR XI and 2.0% in PSUR XII compared to previous periods that never exceeded 0.6% (Bates #00303567). In response to a request from the Swiss Interkantonale Kontrollstelle fur Heilmittel (IKS), in conjunction with the CPMP, three comprehensive reviews of adverse events with sildenafil were compiled by Pfizer:
1) "Sildenafil and Adverse Neurologic, Psychiatric and Selected Vision Events" contained a sub-report titled "Sildenafil and Selected Ocular and Vision Adverse Events" (Dated March 2, 2000) that reported 62 cases of selected retinal adverse events (Bates #002173376).

2) "Sildenafil: Glaucoma, Increased Intraocular Pressure, Retinal Detachment, Retinal Hemorrhage and Blindness" (October 10, 2000) reported 29 non-clinical cases of blindness. A positive rechallenge was reported in one case of a 28-year-old male experiencing temporary blindness on three separate occasions (Bates #003006691-702).
3) "Sildenafil and Anterior Ischemic Optic Neuropathy" reported 26 non-clinical cases of optic neuritis (Bates #003283877).

On July 15, 2005, a Pfizer report for South Africa entitled "Sildenafil and Ischemic Optic Neuropathy-Related Events" noted 72 ischemic optic neuropathy events. Specifically, 32 cases of NAION were reported (Bates #00203411-28).

The collective worldwide experience provided clear notice to Pfizer regarding the need for continued product labeling amplifications relating to NAION and the obligation to initiate/conduct clinical trials to further define this life-altering adverse event.

5. Labeling Chronology

The sole labeling change relating to NAION took place in July 8, 2005 when information was added to the Precaution/Information for Patients section of the U.S. prescribing information. In his June 24, 2005 letter to Lester Crawford, Senator Grassley notes:

> "According to internal FDA documents, Pfizer resisted the FDA's initial request to update the Viagra label to include information about NAION risks. It appears that the company may have relented after it learned that CBSNews would be doing a story on the possible link between NAION and Viagra..." (See Grassley)

The NAION Precaution was later added to the Revatio labeling on November 3, 2005.

As noted later in this section, the foreign Viagra inserts contain information relating to NAION throughout the labeling. Moreover, the Viagra SPC for the United Kingdom was updated on June 8, 2006 to include a Contraindication for patients with previous episodes of NAION and the warnings/precautions and undesired effects sections were altered relating to NAION (See © European Medicines Agency, 2008). Notwithstanding the recent accumulation of Viagra-related NAION events and information, Pfizer has not amplified the U.S. label since 2005.

A labeling chronology is provided below that notes only the specific vision-related additions and deletions to each label. Below are the major labels relating to changes in information for vision loss and NAION:

U.S. Approval Label (from 1999 PDR dated May 1998)
U.S. Label Dated November 24, 1998
U.S. Label Dated September 19, 2002
U.S. Label Dated July 8, 2005
and
Comparison of U.S Label to U.K. Label, Both Dated August 2008

U.S. Approval Label (from 1999 PDR dated May 1998):

CLINICAL PHARMACOLOGY

A comprehensive battery of visual function tests was conducted at doses up to twice the maximum recommended dose. Mild, transient, dose-related impairment of color discrimination (blue/green) was detected using Farnsworth Munsell 100-hue test, with peak efforts near the time of peak plasma levels. This finding is consistent with thee inhibition of PDE6, which is involved in phototransduction in the retina. In flexible titration studies of 4 to 26 weeks, 3% of patients on sildenafil reported visual disturbances described as color tinge or light sensitivity, compared with such finding in placebo-treated patients.

ADVERSE REACTIONS

... Table 1. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*Abnormal Vision: Mild and transient predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

... In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

U.S. Label Dated November 24, 1998:

CLINICAL PHARMACOLOGY

Effects of VIAGRA on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, electroretinograms, intraocular pressure, or pupillometry. ~~A comprehensive battery of visual function tests was conducted at doses up to twice the maximum recommended dose. Mild, transient, dose-related impairment of color discrimination (blue/green) was detected using Farnsworth Munsell 100 hue test, with peak efforts near the time of peak plasma levels. This finding is consistent with thee inhibition of PDE6, which is involved in phototransduction in the retina. In flexible titration studies of 4 to 26 weeks, 3% of patients on sildenafil reported visual disturbances described as color tinge or light sensitivity, compared with such finding in placebo treated patients.~~

ADVERSE REACTIONS

Pre-Marketing Experience

... Table 2 ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
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Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*Abnormal Vision: Mild and transient predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

... In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

Post-Marketing Experience

Ocular: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema.

U.S. Label Dated September 19, 2002:

CLINICAL PHARMACOLOGY

Effects of VIAGRA on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, electroretinograms, intraocular pressure, or pupillometry.

ADVERSE REACTIONS

Pre-Marketing Experience

...Table 2 ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

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Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*Abnormal Vision: Mild and transient predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

... In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

Post-Marketing Experience

~~Ocular~~ Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema.

PATIENT SUMMARY OF INFORMATION ABOUT VIAGRA TABLETS

POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause some side effects. These effects are usually mild to moderate and usually don't last longer than a few hours. Some of these side effects are more likely to occur with higher doses. The most common side effects of VIAGRA are headache, flushing of the face, and upset stomach. Less common side effects that may occur are temporary changes in color vision (such as trouble telling the difference between blue and green objects or having a blue color tinge to them), eyes being more sensitive to light, or blurred vision.

U.S. Label Dated July 8, 2005:

CLINICAL PHARMACOLOGY

Effects of VIAGRA on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, ~~electroretinograms,~~ intraocular pressure, or pupillometry.

PRECAUTIONS

Information for Patients

Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see POST-MARKETING EXPERIENCE/Special Senses).

ADVERSE REACTIONS

Pre-Marketing Experience

... Table 2 ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
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Abnormal Vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

*Abnormal Vision: Mild and transient predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

... In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

Post-Marketing Experience

Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical

defects, to a combination of these factors, or to other factors (see **RECAUTIONS/Information for Patients).**

PATIENT SUMMARY OF INFORMATION ABOUT VIAGRA TABLETS

What to Tell Your Doctor Before you Begin Viagra

Be sure to tell your doctor if you:

• have ever had severe vision loss

POSSIBLE SIDE EFFECTS

Like all medicines, VIAGRA can cause some side effects. These effects are usually mild to moderate and usually don't last longer than a few hours. Some of these side effects are more likely to occur with higher doses. The most common side effects of VIAGRA are headache, flushing of the face, and upset stomach. Less common side effects that may occur are temporary changes in color vision (such as trouble telling the difference between blue and green objects or having a blue color tinge to them), eyes being more sensitive to light, or blurred vision.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including VIAGRA) reported a sudden decrease or loss of vision in one or both eyes. It is not possible to determine whether these events are related directly to these medicines, to other factors such as high blood pressure or diabetes, or to a combination of these. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including VIAGRA, and call a doctor right away.

Comparison of U.S Label to UK Labeling, Both Dated August 2008:

U.S. Label Dated August 2008	UK Labeling Dated August 2008
CLINICAL PHARMACOLOGY **Effects of VIAGRA on Vision:** At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, intraocular pressure, or pupillometry.	**5.1 Pharmacodynamic properties** Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100mg) demonstrated no significant changes in visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).
No Contraindications in U.S. label.	**4.3 Contraindications** VIAGRA is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4). The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of

	retinal phosphodiesterases).
PRECAUTIONS **Information for Patients** Physicians should advise patients to stop use of all PDE5 inhibitors, including VIAGRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors **(see POST-MARKETING EXPERIENCE/Special Senses).**	**4.4 Special warnings and precautions for use** Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking VIAGRA and consult a physician immediately (see section 4.3).
ADVERSE REACTIONS Pre-Marketing Experience Table 2 Adverse Event % Viagra (N=734) Abnormal Vision* 3% *Abnormal Vision: Mild and transient predominantly color tinge to vision , but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently. Post-Marketing Experience	**4.8 Undesirable Effects** Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through post-marketing surveillance **Table 1:** **MedDRA System Organ Class: Adverse Reaction** **Eye disorders** Common: Visual disorders, Visual colour distortion Uncommon: Conjunctival disorders, Eye disorders, Lacrimation disorders, Other eye disorders Not known: Non-arteritic anterior ischaemic optic neuropathy (NAION),

Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction, paramacular edema and epistaxis. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including VIAGRA. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors (see **PRECAUTIONS/Information for Patients).**	Retinal vascular occlusion, Visual field defect.

6. Conclusions

Significant numbers of men choose to use Viagra as a treatment for erectile dysfunction. As such, it is imperative that accurate risk information be contained in the product labeling so that patients and prescribers can make informed decisions relating to elective use of a prescription drug product. An association between use of Viagra and a number of serious and even irreversible ophthalmologic-related adverse events was apparent even prior to its regulatory approvals. Evidence can be found in the growing collection of both internal and public documents discussing the occurrence of adverse events such as blindness, ischemic optic neuropathy, non-arteritic ischemic optic neuropathy, retinopathy, glaucoma and many other others. Sources of information which contributed to this knowledge included the medical literature and spontaneous adverse event databases in the United States and Europe.

Despite an accumulating knowledge of potentially serious ophthalmologic adverse events, Pfizer avoided timely updates to the Viagra product label thereby exposing users to unnecessary and unknown risks. This is especially concerning because a significant percentage of the patient population receiving Viagra possesses one or more risk factors which may predispose them to NAION and related events. Although Pfizer did update the Viagra product label in July 2005, this change does not adequately reflect the number and severity of the serious ophthalmologic events associated with the drug over three years later.

Pfizer long-refused to conduct an appropriately designed study aimed at determining the relatedness of ophthalmologic adverse events (NAION) to Viagra use, while simultaneously citing the dearth of available data on this relationship. In fact, only now is Pfizer initiating a study to examine the incidence of NAION associated with the use of Viagra using a process suggested by FDA several years earlier. Notwithstanding accumulating data, Pfizer has minimized these risks by repeatedly asserting that there is no proven link between these adverse events and use of Viagra. They instead choose to diminish the available findings by citing the often-repeated litany of reasons used to discredit spontaneous adverse event reports. These include background incidence rates,

lack of causality documentation and other potential risk factors found in the patient populations using the drug. Pfizer's behavior has likely resulted in the exposure of numerous patient populations to unnecessary risks associated with Viagra. This is especially egregious since the drug is primarily employed for an elected, lifestyle-based use only.

EXHIBIT 1

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* Generic, OTC, Rx and Biotech pharmaceutical industry knowledge * Executive and consultant experience in private/publicly held pharmaceutical companies * Drug discovery/device/ pharmaceutical product development * NDA/ANDA/IND/BLA compilation/submission * Product launch strategies * Europe and United States government registrations/regulatory affairs * FDA interactions * Expert witness in clinical pharmacology, toxicology and in pharmaceutical related litigation * U.S. Patent/trademark submission/approval procedures * Pre-clinical and clinical development * Analytical/Bioanalytical laboratory development/management * Design, planning, and implementation of pivotal pre-clinical and clinical trials * Quality assurance management
* Establishment and implementation of Good Laboratory and Good Manufacturing Practices
* Regulatory oversight of sales and marketing programs

SUMMARY

Generic and ethical pharmaceutical development and registration strategist with more than 25 years experience including independent consultant to national and international pharmaceutical firms, expert witness in national pharmaceutical litigation, as well as executive positions in generic and ethical pharmaceutical companies. Accomplishments in complete NDA, ANDA, IND and BLA development, submission, approval, market launch and post-approval programs with extraordinary results. Successful in the development, implementation and direction of Regulatory Affairs, Pre-Clinical and Clinical Development, Pharmacokinetics, Statistics, Quality Assurance, Analytical and Bioanalytical Laboratories, Document Control, Marketing Oversight and Professional Services.

HIGHLIGHTS/ACCOMPLISHMENTS

- As an independent consultant, formulate international and national pharmaceutical development programs, evaluate clinical and preclinical data and direct the elaboration and prosecution of government registration dossiers. Expert witness in national pharmaceutical litigation relating to product launches, product related liabilities, pharmaceutical adverse medical events, market definitions, product labeling and registration activities. Assist counsel in developing strategies relating to regulatory and marketing elements associated with litigation. Serve as clinical pharmacology, regulatory affairs and toxicology expert witness.

- Spearheaded research and development, submission and approval programs for three complete New Drug Applications (NDA) with accumulated United States sales exceeding $2 billion. FDA approved two of these NDAs within one year of submission. Accountable for several additional new product launches in the United States.

- Directed new product development, submission and approval of more than 100 Abbreviated New Drug Applications (ANDA) with the majority being the first generic approval granted by FDA.

- Accountable for the submission of at least 30 Investigational New Drug Applications (IND) that permitted initiation of clinical trials in the United States in the following areas: Cardiology, Neurology, Psychiatry, Pediatrics, Gastroenterology, Infectious Disease, Oncology, Dermatology, and Topical Analgesia.

- Inventor of record for 30 United States and foreign cardiovascular, neurologic and psychiatric product and method of use patents, as well as several pending applications.

- Ultimate responsibility for the design, development, implementation, finalization and submission of Phase I-IV clinical and all phases of toxicology trials to FDA and other regulatory scientific review bodies.

- Experienced in the design of development programs for oral, topical, transdermal and parenteral dosage forms.

- Successful in interacting with contract research organizations and all subsidiary and external manufacturers (bulk and finished product), formulators, packagers, and other suppliers of goods and services.

- Appeared before the United States House of Representatives, Wall Street, Financial Analysts meetings, national Pharmaceutical Association Meetings and on local and national television.

- Expert pharmaceutical witness in multiple national and international judicial proceedings.
- Author of multiple peer reviewed pharmaceutical and medical related articles.
- Responsible for the regulatory oversight of the sales and marketing development and implementation programs for generic, OTC and prescription drug products.

PROFESSIONAL EXPERIENCE

Pharmaceutical Development Group, Inc. Tampa, Florida
1999 to Present
President

University of South Florida College of Medicine Tampa, Florida
2007 to 2009
Affiliate Associate Professor to the Voluntary Faculty of the Department of Molecular Pharmacology & Physiology

University of South Florida College of Medicine Tampa, Florida
2004 to 2007
Affiliate (Research Scientist) Associate Professor to the Voluntary Faculty of the Department of Pharmacology

Somerset Pharmaceuticals, Inc. Tampa, Florida
1993 to 1998
Executive Vice President/Chief Operations Officer
Board of Directors
Vice President

Mylan Laboratories, Inc. Morgantown, West Virginia/Tampa, Florida
1977 to 1995
Vice President
Technical Director
Director of Pharmacology/Assistant Director of Regulatory Affairs

EDUCATION

West Virginia University – **Bachelor of Arts Degree in Biology**
West Virginia University School of Medicine – **Doctorate Degree in Medical Pharmacology**

- Phi Beta Kappa (National Scholastic Honorary)
- Recipient NIH Pre-Doctoral Fellowship

AWARDS/ORGANIZATIONS

- West Virginia University Alumni Association
- Active member of Phi Beta Kappa Alumni Association
- American Pharmacists Association
- Academy of Pharmaceutical Sciences
- Elected in 1997 to the Board of Fellows at the University of Tampa
- Affiliate (Research Scientist) Associate Professor to the Voluntary Faculty of the Department of Molecular Pharmacology & Physiology – University of South Florida.
- Regulatory Affairs Professionals Society (RAPS)
- International Society for Pharmacoepidemiology (ISPE)
- Drug Information Association (DIA)

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▪ E-mail: cblume@pharmdevgroup.com

AWARDED PATENTS

- Patent No. US4,444,769 - Antihypertensive diuretic combination composition and associated method
- Patent No. US4,526,777 - Pharmaceutical combination composition and associated method
- Patent No. US4,547,498 - Pharmaceutical combination composition and associated method
- Patent No. PH21520-Antihypertensive diuretic combination and associated method
- Patent No CA1220423-Pharmaceutical combination composition and associated method
- Patent No. EP0207405-Method for making pharmaceutical combination composition in granularity heterogenous solid unit dosage form with enhanced bioavailability.
- Patent No.AT51147T-Verfahren zur herstellung einer kombinierten pharmazeutischen zusammensetzung in einer granulaeren heterogenen dosisform mit erhoehter bioverfuegbarkeit
- Patent No. AT29663T-Kombinierte pharmazeutische zusammensetzung und zugehoeriges verfahren
- Patent No. US6,299,901 - Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. US6,348,208 - Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. US6,419,948 - R(-)desmethylselegiline and its use in transdermal delivery compositions
- Patent No. US6,528,082 - Methods and pharmaceutical compositions employing desmethylselegiline to treat neoplastic diseases or conditions
- Patent No. US6,562,364 – Desmethylselegiline enantiomers and their use to treat drug withdrawal symptoms
- Patent No. US6,562,365 - Methods employing R(-)-desmethylselegiline
- Patent No. US6,699,495 - Methods for treating multiple sclerosis employing desmethylselegiline
- Patent No. WO03075906-Methods for preventing and treating peripheral neuropathy by administering desmethylselegiline.
- Patent No. WO0219964-Methods and pharmaceutical compositions employing desmethylselegiline to treat neoplastic diseases or conditions

- Patent No. AU9235898– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. AU719447B- Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. NO973261- Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. WO9622068- Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. AU695359B– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. CA2,209,892– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. CN96192486.1– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. JP3036847– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. FI972988– Methods and pharmaceutical compositions employing desmethylselegiline
- Patent No. AU709447–Methods and pharmaceutical compositions employing desmethylselegiline

PUBLICATIONS

- Absorption and disposition of a low-dose combination formulation of hydrochlorothiazide and triamterene. Biopharm Drug Dispos. 1990 Apr;11(3):233-43. Williams RL, Lin ET, Liang-Gee W, Blume CD, Benet LZ.
- Effects of formulation and food on the absorption of hydrochlorothiazide and triamterene or amiloride from combination diuretic products. Pharm Res. 1987 Aug;4(4):348-52. Williams RL, Mordenti J, Upton RA, Lin ET, Gee WL, Blume CD, Benet LZ.
- Absorption and disposition of two combination formulations of hydrochlorothiazide and triamterene: influence of age and renal function. Clin Pharmacol Ther. 1986 Aug;40(2):226-32. Williams RL, Thornhill MD, Upton RA, Blume C, Clark TS, Lin E, Benet LZ.
- Absence of a significant pharmacokinetic interaction between hydrochlorothiazide and triamterene when coadministered.J Pharmacokinet Biopharm. 1984 Dec;12(6):575-86. Upton RA, Williams RL, Lin ET, Gee WL, Blume CD, Benet LZ.
- Pharmacokinetic-pharmacodynamic analysis of unbound disopyramide directly measured in serial plasma samples in man. J Pharmacokinet Biopharm. 1984 Dec;12(6):559-73. Thibonnier M, Holford NH, Upton RA, Blume CD, Williams RL.
- Bioequivalence study of a tablet formulation of triamterene and hydrochlorothiazide.
  Am J Med. 1984 Nov 5;77(5A):59-61. Blume CD, Williams RL, Upton RA, Lin ET, Benet LZ.
- Clinical experience with a combination formulation of triamterene and hydrochlorothiazide (Maxzide) in patients with mild to moderate hypertension.Am J Med. 1984 Nov 5;77(5A):62-6. Williams RL, Clark T, Blume CD.
- A antihypertensive agent: Maxzide (75 mg triamterene/50 mg hydrochlorothiazide).
  Am J Med. 1984 Nov 5;77(5A):52-8. Blume CD, Williams RL.
- Relative bioavailability of chlorthalidone in humans: adverse influence of polyethylene glycol.
  J Pharm Sci. 1982 May;71(5):533-5. Williams RL, Blume CD, Lin ET, Holford NH, Benet LZ.
- Comparative effects and mechanisms of castration, estrogen anti-androgen, and anti-estrogen-induced regression of accessory sex organ epithelium and muscle. Invest Urol. 1981 Jan;18(4):229-34. Neubauer B, Blume C, Cricco R, Greiner J, Mawhinney M.
- Estrophilic molecules in the male guinea pig. J Steroid Biochem. 1978 Jun;9(6):515-25. No abstract available. Blume CD, Mawhinney MG.
- Androphilic and estrophilic molecules in canine prostate glands. Invest Urol. 1978 Mar;15(5):425-31. No abstract available. Robinette CL, Blume CD, Mawhinney MG.

- Androgen and estrogen binding in male guinea pig accessory sex organs. Endocrinology. 1977 Sep;101(3):726-40. No abstract available. Belis JA, Blume CD, Mawhinney MG.

EXHIBIT 2

LIST OF REVIEWED MATERIALS

Pfizer Production Documents

- Pfizer production documents provided in hard drive and CD.
- Pfizer production documents such as sildenafil related study reports and FDA correspondence

Medical literature

- Literature regarding adverse events associated with sildenafil-containing products (Viagra® and Revatio®)
- Other scientific literature regarding the etiology of opthalmological disorders, including NAION, associated with PDE-5 inhibitors.

Regulatory Information

- 21 CFR 314.80; 21 CFR 313.32(b); 21 CFR 312.33(f); Form FDA 356h
- Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005
- Pharmaceutical Labels
- Other FDA (including DDMAC) and foreign regulatory documents including but not limited to Federal Register Notices, reports, papers, surveys, meeting minutes, regulatory correspondences and other regulatory documents available on internet websites.

Depositions

- Depositions of multiple Pfizer employees, staff and consultants.
- Depositions of Stephen Watt, Stephen Kimmell, Sohan Hayreh, Rachel Sobel, Peter Netland, Peter Ellis, John Gamel, Ian Osterloh, Howard Pomeranz, Gregory Gribko, Gerald McGwin and Augustine Aruna

Plaintiff Specific Documents

- Plaintiff's petition (complaint)